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Patent- og
Varemærkestyrelsen
Erhvervsministeriet

Taastrup, 18 October 2000


Karin Schlichting
Head Clerk

TITLE

Wound care device

FIELD OF THE INVENTION

The present invention relates to a wound care device comprising chitosan, said
5 chitosan being capable of absorbing liquid to form a swollen, coherent gel, and a
method of preparation of the same.

BACKGROUND OF THE INVENTION

In the treatment of exuding wounds there is a need for an absorbent dressing
being capable of adapting to the conformation of the individual wound. This is
10 fulfilled done by using fibre dressings or hydrogels.

Wound care devices comprising fibres may be based on polysaccharide fibres,
which are usually water insoluble, but water absorbing. They are in general based
on alginate, CMC or chitosan. Wound care products such as dressings or fillers
based on alginate, CMC or chitosan fibres, may be able to absorb up to 20-25 g
15 exudate/gram product, with limited swellability and gellability. These fibre
dressings/fillers are normally supplied in sterilised.

The use of fibres often suffers from the drawback of a limited absorption and/or
lack of cohesion, leading to difficulties with respect to removing the fibre product
from the wound as the product does not constitute a cohesive part.

20 Methods of preparing alginate fibres are well known. Normally sodium alginate is
completely converted into insoluble calcium alginate fibres. Methods for enhanc-
ing the solubility of alginate fibres are also well known. International Patent Appli-
cation No. WO 94/17227 discloses a method for preparing highly absorbent
alginate fibres by conversion of calcium alginate fibres into alginic acid fibres.

In International Patent Application No. WO 94/16746 is disclosed a process of preparing carboxy methyl cellulose fibres which are gellable, but still coherent enough to be removed from a wound in one piece.

- European Patent Application No. 627 225 discloses a method for preparing a
- 5 superabsorbent chitosan powder, being capable of absorbing liquid many times its own weight by forming a transparent gel. This is done by treating the powdery chitosan with an acid, preferably a hydroxy carbon acid like lactic acid or hydroxy butyric acid. The resulting powder is capable of absorbing high amounts of water by forming a gel.
- 10 The acid-modified chitosan disclosed in EP 627 225 A2 is suitable for use as a superabsorbent in diapers and like products, in which the powdered material will be encapsulated and little or no coherence is demanded. The reference is silent with respect to preparation of highly coherent material, for use in e.g. wound care products.
- 15 Published Japanese Patent Application No. JP 9-69654-A discloses a method for preparing partly deacetylated chitin fibre for wound care. The preferred chitin material has a deacetylation degree of max. 90 %, preferably 40 - 60 %. The material is not used as an absorbent, but as a haemostatic agent for stopping bleeding wounds.
- 20 Thus, there still is a need for a wound care device comprising a material being capable of absorbing large amount of liquid by gelling, and having a high degree of cohesion after absorption. The need is fulfilled by the wound care device of the present invention.

BRIEF DESCRIPTION OF THE INVENTION

- 25 The present Invention relates to a wound care device comprising chitosan, said chitosan being capable of absorbing liquid to form a swollen, coherent gel, and said chitosan having been modified by treatment with acid and heat.

The present invention further relates to a method of preparation of a wound care device comprising chitosan being capable of absorbing liquid to form a swollen, coherent gel.

DETAILED DESCRIPTION OF THE INVENTION

- 5 The invention relates to a wound care device comprising chitosan, said chitosan being capable of absorbing liquid to form a swollen, coherent gel, and said chitosan being in the form of fibres having been modified by treatment with acid and heat.

- The fibrous structure of the chitosan according to the present invention may
10 provide a essential coherence for use in a wound dressing. When used as e.g. a wound contacting fabric, it is important that the absorber is coherent rendering it possible to remove the wound dressing in one piece from the wound.

- Chitosan fibres may be used as raw material. In principle, all chitosan fibre may be used. The preparation of the modified chitosan fibres according to the inven-
15 tion may be optimised depending on the quality of the raw material. Parameters such as fibre diameter, molecular weight of chitosan, degree of deacetylation and source or origin of the chitosan may influence on the process.

Chitosan fibres are usually made from chitosan of a low molecular weight.

- It is preferred that the molecular weight of the chitosan used for the preparation of
20 the wound care device according to the present invention is less than 750.000, more preferred less than 400.000, and even more preferred less than 250.000, and most preferred less than 175.000.

Most preferred is chitosan with a molecular weight lower than 300.000.

Chitosan fibres suitable for use in this invention are fibres with a deacetylation degree above 65 %, more preferred above 75 % and most preferred above 85 %.

Preferably, the fibres are having a minimum average length of 3 mm. The preferred proportion between length and diameter of the fibres is at least 25,
5 more preferred at least 80 and most preferred at least 200.

The invention also relates to a method of preparation of a wound care device comprising chitosan being capable of absorbing liquid to form a swollen, coherent gel, said method comprises the steps of

- a) suspending the chitosan in the form of fibre in a non-solvent comprising acid
- 10 b) isolating the resulting modified chitosan from the non-solvent
- c) treating the chitosan with heat during step a) or/and b).

The chitosan is according to the present invention modified by treatment with acid and heat. This treatment is converting the chitosan fibres in a water insoluble, non swelling and non gelling state into chitosan fibres which are water swelling, water
15 gelling but still substantially water insoluble and with a coherent structure.

By the terms water swelling, water gelling but substantially water-insoluble is meant that when the fibres are contacted with an aqueous liquid, such as wound exudate, they will absorb liquid and swell by forming a gel. The fibre structure will still be detectable. The fibres will turn from non-transparent into relative transparent
20 ent fibres. The fibres are not completely water-insoluble (few molecules may dissolve), but the material is sufficient water-insoluble and coherent to render it possible to remove the fibres from a wound in one piece.

The non-solvents used according to the present invention may be any non-solvent to chitosan, preferably a non-solvent with a boiling point higher than
25 50 °C and even more preferred non solvents with a boiling point between 60 and 250 °C.

Acids suitable for this embodiment of the invention are any low molecular organic acid.

The preferred acids are organic acids such as formic, acetic, halogen acetic acids (such as fluoro or chloro acetic acid), propanoic, propenoic, lactic, acrylic glyoxylic, pyruvic or a hydroxy propionic/butanic acid.

The more preferred organic acids used for modification of the chitosan fibre in the wound care device according to the invention may be a hydroxy or acyl organic acid, which is soluble in the used non-solvent, preferably glucolic, glyoxylic, pyruvic, lactic or a hydroxy propionic/butanic acid.

10 The most preferred acid is lactic acid.

Preferably, the quantity of acid used in the modification process according to the present invention is from 2 mmol to 20 mmol per gram chitosan, more preferred from 3 to 15 mmol acid per gram chitosan and most preferred from 4 to 10 mmol acid per gram chitosan. Higher amounts of acid will not change the result in
15 neither a positive nor negative way, and is therefore considered to be unnecessary.

The heat treatment of the chitosan fibre may be conducted at any temperature above 50 °C.

The preferred temperature of the heat treatment of the chitosan fibre is between
20 50 - 250 °C, more preferred from 60 to 225 °C.

The modified fibres according to this invention have preferably an absorption higher than 20 g/g, more preferred higher than 25 g/g and most preferred higher than 30 g/g.

The wound care device according to the invention may be in the form of a fibre rope, woven, knitted or non-woven sheets or pouches or it may be in the form of an island dressing, with an absorbent centre part based on the modified chitosan fibres and an adhesive film covering and extending further than the absorbent part.

The wound care device according to the invention may be based on a woven or non-woven fabric comprising the modified chitosan fibres, which is water swellable and gellable.

The wound dressing may have a minimum absorption of 0.20 g/cm².

10 The absorption of the wound care device according to the invention is preferably minimum 0.20 g/cm², more preferred minimum 0.25 g/cm² and most preferred more than 0.30 g/cm².

If the modified chitosan fibres are preferably in the form of a wound cavity filler such as a fibre rope, the total absorption of the rope is more than 20 g/g,

15 preferred more than 25 g/g and most preferred more than 30 g/g.

The wound care device according to the present invention is especially suitable for treatment of leg ulcers, burns, pressure sores, diabetic ulcers, cancer wounds and acute wounds.

In a first embodiment of the invention the acid treatment and the heat treatment is a combined process, according to which the chitosan fibres may be treated with acid under simultaneous heat treatment

In the first embodiment of the invention the temperature of which the acid treatment is processed is preferably from 50 to 200 more preferred from 60 to 180 °C and most preferred from 64 to 160 °C.

In a second embodiment of the invention, the acid is a mixture of at least two acids.

The first acid may be a hydroxy organic acid, which is soluble in the used solvent, preferably glucolic or a hydroxy propionic/butanic acid. Especially preferred is
5 lactic acid.

When chitosan molecules are treated with acids of the first type at a temperature below 85 °C, very weak and few cross linking point between the chitosan molecules are created. This will turn the chitosan from an insoluble form into almost soluble form with very limited cohesion. If the material is sterilised by
10 radiation this will result in an even lower cohesion. Thus, there is a need for additional cohesion. This may be obtained by adding the second type of acid to the treatment.

The first acid is imparting gelling and swelling ability to the chitosan fibres and the second acid is imparting cohesion to the fibres.

15 The second acid will provide the fibres with substantially insolubility and cohesion. The cohesion is obtained as a result of intermolecular crosslinking between the chitosan molecules, where the chitosan molecules have formed an acid salt with the second acid.

The second acid may be an inorganic sulphur or phosphor acid or any organic
20 acid except hydroxy acids, which is soluble in the used non-solvent. Preferred organic acids may be: Formic, acetic, propanoic, butanoic and propenoic acid. Also halogenated derivative of these such as chloro acetic acid may be used.

It is preferred that the second acid is an inorganic sulphur or phosphor acid or one of following organic acid: Formic, acetic, propanoic, butanoic and propenoic
25 acid, or a halogenated derivative of these such as chloro acetic acid.

It is especially preferred that the second acid is formic, acetic, propanoic or propenoic acid.

The first acid may comprise 20 - 100 % of the total acid content, more preferred 40 - 97 % and most preferred 60 - 95 % of the total acid content.

- 5 The second acid may comprise 0 - 80 % of the total acid content of the solution, more preferred 3 - 60 %, and most preferred 5 - 50 % of the total acid content.

It is preferred to let the acid treatment last until the desired level of crosslinking occurs. By reducing the reaction time of the process, the chitosan fibres may have been converted to a chitosan acid salt, but the molecules have not yet
10 crosslinked. This results in more or less water soluble chitosan fibres, which is not desired.

The process time for the combined acid and heat treatment may suitably be more than 2 hours, preferably more than 3 hours.

- 15 If the treatment is prolonged to more than 4 hours, it may be possible to use only acid of the first type, especially if the temperature is below to 85 °C, and still obtain a wound care device with so high cohesion, that removal in one piece is possible.

By combining the above specified first and second acid in the specified amount, the resulting fibres are water swellable and gellable, but still water insoluble
20 rendering it possible that a wound care dressing comprising these modified chitosan fibres may be removed in one piece after having absorbed wound exudate.

Combinations of acids within each group of either first or second acid group may also be applied.

Especially preferred is a mixture of lactic acid and any low molecular weight organic acid (molecular weight < 300 g/mole).

Most preferred is an acid mixture of lactic acid and formic, acetic, propanoic or propenoic acid.

- 5 The combined acid and heat treatment of the chitosan in this embodiment of the invention may be conducted at a temperature of 50 - 85 °C, more preferred from 60 to 85 °C, even more preferred from 64 to 85 °C and most preferred at the boiling point of the non-solvent.

- In a third embodiment of the invention, the acid treatment is conducted at a high
10 temperature, above 85 °C. When the temperature is kept above 85 °C in the acid treatment, only one acid is necessary to achieve the preferred properties of the chitosan fibres.

- The preferred acid used in the modification of the chitosan fibres of this embodi-
ment of the invention is an hydroxy organic acid, which is soluble in the used
15 solvent, preferably glucolic or a hydroxy propionic/butanic acid.

Especially preferred is lactic acid.

Mixtures of acids may also be used.

- The temperature at which the treatment is conducted is preferably from 85 to 200 °C, more preferred from 85 to 180 °C and more preferred from 85 to 160 °C and
20 most preferred from 90 to 160 °C. .

The used non-solvent can be any non-solvent with a boiling point above 85 °C. Most preferred is alcoholic solvents such as propanol, isopropanol and butanol.

The duration of the acid treatment depends of the type and quantity of acid, the quantity of water and the temperature. The process time may vary from seconds to several hours. The higher temperature and quantity of acid and water, the shorter time is needed to achieve the desired properties of the chitosan fibres.

- 5 The higher concentration of acid during the acid treatment, the shorter time is needed to convert the chitosan fibres.

In a fourth embodiment of the invention, the acid treatment is conducted at low temperature. After the acid treatment, the fibres are isolated from the acid solution and subsequently subjected to a heat treatment in an oven at an
10 elevated temperature.

- In general, the acid treatment will turn the chitosan fibres from insoluble and low absorbent into water soluble, or if the acid treatment is limited, partly soluble and partly water insoluble. The solubility is a consequence of that the chitosan molecules are in the acid treatment converted to chitosan acid salts molecules.
15 Therefore the acid treatment influences the subsequent heat treatment and the performance of the modified fibres.

- Acids suitable for this embodiment of the invention are low molecular weight inorganic acids and organic acids such as formic, acetic, halogen acetic acids (such as fluoro or chloro acetic acid), propanoic, propenoic, lactic, acrylic, glyox-
20 ylic, pyruvic or a hydroxy propionic/butanic acid, more preferred organic acid such as formic, acetic, propanoic, propenoic, lactic, acrylic, glyoxylic, pyruvic or a hydroxy propionic/butanic acid.

Most preferred is lactic acid.

- In this embodiment of the invention mixtures of two or more acids is preferred.
25 Most preferred is mixtures of lactic acid and any low molecular weight organic acid (molecular weight below 300 g/mole and soluble in the non-solvent).

The temperature during the acid treatment should be kept so low, that the fibres do not form a gel after the treatment, but dissolve when they are contacted with water.

The temperature during the acid treatment is preferably from the freezing point of the solvent to 80 °C, depending on what temperature the fibres start to gel. The temperature is more preferred kept from -10 to 64°C, and most preferred kept at -10 to 40°C, and most preferred kept at room temperature.

The duration of the acid treatment should be until a sufficient numbers of amine groups have been protonated so the chitosan fibres will form a gel after the heat treatment if contacted with an aqueous liquid. The duration of the acid treatment depend on the amount of water, type of acid, amount of acid and the type, shape or origin of the chitosan.

The size of the chitosan fibres is also important. The larger diameter of the fibres, the longer acid treatment time is needed.

15 The duration of the acid treatment can, depending on the water amount, acid concentration, temperature and chitosan fibre be treated from a few seconds to many hours before the treatment is ended.

By prolonging the treatment to days, there is no harm caused to the fibres (unless the concentration of the acid is so high, that hydrolysis may occur), but the prolonged treatment is unnecessary - when the fibres have become soluble in water, there is no need for continuing the treatment.

If the acid treatment is carried out with 6 % water, ethanol and 7.5 mmol acetic acid per gram chitosan fibres (100 gram non-solvent per 10 gram chitosan fibres), the acid treatment of the chitosan fibres will after only 10 minutes acid treatment at room temperature be almost completely soluble in water.

After the acid treatment the fibres may be washed in an alcohol to remove residual acid and subsequently dried.

- Hereafter the fibres may be subjected to a dry heat treatment. The heat treatment may be carried out at an elevated temperature, preferably from 60 to 250 °C,
- 5 more preferred 80 to 250 °C and most preferred at 100 to 200 °C.

During the heat treatment, the chitosan fibres will turn from water soluble to water swellable, gellable and substantially water insoluble.

- The duration of the heat treatment depends on the temperature of the heat treatment and the choice of acid. If the dry heat treatment is carried out at 100 °C, the
- 10 heat treatment has a duration of preferably ½ to 8 hours, depending of which acid is used. The higher temperature in the heat treatment, the shorter time is needed to convert the fibres from water soluble to swellable, water absorbent and gellable. If the heat treatment is carried out at 175 °C only a few minutes or even seconds are needed to convert the fibres to gellable and more insoluble.

- 15 The more severe heat treatment, the less swellable the fibres becomes. The more gentle heat treatment, the more swellable becomes the fibre, and optionally water soluble. Therefore the heat treatment should be optimised so the chitosan fibres after the heat treatment are water swellable and substantially water insoluble.
- 20 In this embodiment of the invention, it is preferred to conduct the acid treatment at room temperature with 4 to 10 mmole acid, e.g. 80 % lactic acid and 20 % acetic acid, per gram chitosan, rinse the fibres in ethanol and heat treat the fibres at 60 °C in 10 minutes. The fibre are processed into a non-woven fabric, packed and sterilised.

In a fifth embodiment of the invention the chitosan fibres are first treated with acid, and subsequently treated with a base. In this way, the fibres are first converted to water soluble fibres by the acid treatment, and are then turned into water swellable but substantially water insoluble absorbent fibres by the alkaline
5 treatment.

In a sixth embodiment of the invention, the chitosan fibres are treated with heat both during and acid treatment and then again subsequently.

In a seventh embodiment of the invention, the chitosan fibre are acid treated in a limited way only with an acid, resulting in fibres, which are water swellable, water
10 gelling but substantially water insoluble.

By treated in a limited way is meant, that the chitosan fibres are only partly converted into a acid salt, in such a manner that the molecules will expand when they contacted with an aqueous liquid, but still maintain their structure in such a degree, that removal in one piece from a wound is possible.

15 The process of carrying out this embodiment of the invention is preferably by reducing amount of acid in the acid treatment. By doing this, the acid will not be able to complete the conversation of chitosan into a chitosan salt.

In this embodiment the fibres may be treated as in the first and the second embodiment of the invention, but only with a minimal amount of acid. The amount
20 of acid is from 2 to 7 mmole acid per gram chitosan preferably 3 - 7 mmole acid per gram chitosan and most preferred from 4 to 6.5 mmole acid per gram chitosan.

The fibre are optionally treated with acids of the first type. The most preferred acid is lactic acid.

25 In an eighth embodiment of the invention, the used chitosan fibres are "never-dried" chitosan fibres. By using "never-dried" chitosan fibres, the process for

modifying the fibre may be adjusted in such a manner, that water absorbent, gellable and substantially water insoluble fibres still may be obtained after the modification process. This is preferably done by treating the fibres more gentle than if dried fibres were used in the modification process.

- 5 In a ninth embodiment of the invention strength is added to the modified chitosan fibres by adding anionic fibres.

In a wound care device more strength and cohesion may be desired. This may be obtained by adding fibres other than chitosan to the device. These fibres may be blended with the chitosan fibres or be woven, or be in separate layers.

- 10 These anionic fibres may be fibres such as alginate or carboxy methyl cellulose fibres. When the anionic fibre are added to the modified chitosan fibres, they will, when the fibres are contacted with wound exudate, open up their structure and a crosslinking between the anionic molecule group and the modified chitosan molecule group will occur.
- 15 The amount of anionic fibres in a wound care device according to the present invention is preferably between 5 and 60 % and more preferred between 10 and 50%.

- The process of adding anionic fibres could be any suitable process, one example of such a process could be by carding both the modified chitosan and the anionic
- 20 fibres into a carded fibre mixture.

An other way of manufacturing could be to make yarn of both the modified chitosan and the anionic fibre and weave the fibres into a woven fabric.

- In a tenth embodiment of the invention, the modified chitosan fibres are mixed with unmodified chitosan, cotton, wool or viscose fibres or the like, and processed
- 25 into a woven or non-woven fabric, obtaining a product which is water insoluble

and low absorbent cotton, wool or viscose and water gellable, water swellable, highly water absorbent and substantially water insoluble modified chitosan fibres.

The above mentioned fabric may be manufactured by mixing the chitosan and the other fibres before or after the modification of the chitosan. The fibres may be
5 spun into a yarn of e.g. cotton and chitosan, comprising preferably 5 - 95 % modified chitosan and more preferably 10 - 90 % modified chitosan, and most preferred 25 - 75 %, depending on the use of the fabric.

If the fabric is to be used for low exuding wounds, a dressing with a low amount of modified chitosan fibres is desired, but if the fabric is to be used on highly exuding
10 wounds, a higher amount of modified chitosan fibres is requested.

The process of preparing this embodiment of the invention may be the same process as described in the 9th embodiment of the invention.

An other process of preparing the wound care device may be to process chitosan fibres into yarn and then modify the chitosan yarn to obtain yarn of modified chito-
15 san. The yarn is weaved with any of the above described nonionic fibres.

In both the ninth and the tenth embodiment of the invention less cohesive modified chitosan fibre may be used, as the added non modified chitosan fibres will provide strength and cohesion to the resulting wound care device.

In an eleventh embodiment of the invention the chitosan material could be
20 present in the form of powder, then first modifying chitosan powder with acid and heat, and then process the modified powder particles into fibres. The modified fibre are subsequently processed into a wound care device.

In a twelfth embodiment of the invention the modified chitosan fibres are processed into a non-woven fabric. The non-woven fabric may be formed by
25 randomly laying, for example dry-laying, or crosslaying the fibres followed by needling. An alternative non-woven fabric may be formed by crosslaying the

modified chitosan fibres while partially moist, followed by drying, optionally under pressure.

The non-woven product may be used as a wound dressing or as a wound contacting layer of a wound care product.

- 5 In a thirteenth embodiment of the invention the wound care device comprises one or more active ingredients, e.g. a pharmaceutical medicament. This opens for a combined medical treatment of a wound, where the fibres absorb wound exudate and the pharmaceutical medicaments will be applied to the wound. The pharmaceutical medicaments will either be incorporated in the wound care device or
- 10 migrate to the wound surface and promote its function. .

- Examples of such pharmaceutical medicaments includes a cytokine such as a growth hormone or a polypeptide growth factor such as TGF, FGF, PDGF, EGF, IGF-1, IGF-2, colony stimulating factor, transforming growth factor, nerve stimulating growth factor and the like giving rise to the incorporation of such active
- 15 substances in a form being apt to local application in a wound in which the medicament may exercise its effect on the wound, other medicaments such as bacteriostatic or bactericidal compounds, e.g. iodine, iodopovidone complexes, chloramine, chlorohexidine, silver salts such as sulphadiazine, silver nitrate, silver acetate, silver lactate, silver sulphate, silver sodium thiosulphate or silver
- 20 chloride, zinc or salts thereof, metronidazol, sulpha drugs, and penicillin's, tissue-healing enhancing agents, e.g. RGD tripeptides and the like, proteins, amino acids such as taurine, vitamins such ascorbic acid, enzymes for cleansing of wounds, e.g. pepsin, trypsin and the like, proteinase inhibitors or metalloproteinase inhibitors such as Illostat or ethylene diamine tetraacetic acid, cytotoxic
- 25 agents and proliferation inhibitors for use in for example surgical insertion of the product in cancer tissue and/or other therapeutic agents which optionally may be used for topical application, pain relieving agents such as lidocaine or chincho-caine, emollients, retinoids or agents having a cooling effect which is also considered an aspect of the invention.

In a fourteenth embodiment of the invention, the chitosan fibres are partly carboxy methylated, and due to this turned from insoluble and low absorbent and into highly absorbent, gelling and substantially water insoluble. This is achieved by treating the chitosan fibres with a water/alcohol solution containing sodium hydroxide and the sodium salt of chloro acetic acid. The treatment is carried out at an elevated temperature.

The temperature and time of the treatment will depend of the concentration of the sodium hydroxide, water and the sodium salt of chloro acetic acid. However a preferred temperature for the treatment may be 40 to 180 °C, more preferred 50 to 140 and most preferred 50 to 120 °C.

The duration of the treatment depends on the process parameters, however the preferred reaction time is from 1 minute to 24 hours.

If the fibres are completely carboxy methylated, the fibres will become water soluble and thus not useful as such in a wound care dressing demanding coherence. Therefore it is important that the chitosan fibres only are partly carboxy methylated, so the chitosan fibre become water absorbent, water swellable and substantially water insoluble.

The preferred degree of carboxy methylation should be between 0.1 and 0.9, more preferred from 0.25 to 0.75 and most preferred from 0.3 to 0.6 (the number refers to how many carboxy methyl units there are per monosaccharide).

The process of partly carboxy methylate chitosan fibres could be any suitable process, such as treating the chitosan fibre with a mixture of an alcohol, water, sodium hydroxide and the sodium salt of chloro acetic acid.

The invention is explained more in detail in the working examples below disclosing embodiments and properties of the wound care device of the invention. It is

evident that many variations may be made without diverging from the invention the scope of which is set forth in the appended claims.

EXAMPLES:

Method of measuring absorption of free fibres in water

- 5 A weighted (W1) amount (app. 0.2 grams) of the fibre sample was cut and put into a bag made of polyethylene net. Then the sample was placed in a vessel containing excess amounts of solution A (142.5 mM NaCl and 2.5 mM CaCl₂). After one hour the sample was removed from the solution and held over the solution for ½ minute, whereafter the weight was measured (W3) and the sample
10 was returned into the vessel. After 24 hours, again the weight of the sample was measured as before (W4). The weight of a wet, empty PE-net bag was also measured (W2). W2 is a average value of 10 measurements.

The absorption of the a fibre sample was calculated as:

Absorption after 1 hour (g/g):

$$15 \quad (W3-W2-W1)/W1$$

Absorption (after 24 hours) in g/g:

$$(W4-W2-W1)/W1$$

The absorbency of a non-woven fabric:

- A piece of 4x4 cm was cut and weighted (W1). The sample was put into a petri
20 dish containing excess solution A for 4 hours. Hereafter the sample was removed and allowed to drip off for ½ minute, whereafter the weight was measured (W2).

The absorption (in g/cm²) was calculated as:

$$(W2-W1)/16$$

Cohesion of the modified chitosan fibres:

- 25 This test method is a qualitative measurement of the gellability, solubility and cohesion of wet fibre samples.

A fibre sample was soaked saline water (solution A) for 24 hours. After the 24 hours, the sample was qualitatively evaluated and categorised into one of following categories:

- 0 The sample is completely water soluble. The absorption is not measurable as
5 the sample dissolves out of the PE-net.
- 1 The sample is almost water soluble with only limited gellability. The cohesion of the gel is extreme low. The absorption may be measurable, but still some parts of the sample may have dissolved out of the PE-net.
- 2 The sample is partly water swellable and partly gellable. Some chitosan
10 molecules seems to dissolve (the gel is greasy). The fibre structure is slightly visible after absorption. The gelled mass has some cohesion, so removal in one piece may be possible.
- 3 The sample is gelled. The fibres are cohesive, water swellable and transparent. The gelled fibre still maintain their fibre structure and removal in one piece is easy
15 to obtain. The fibres are no longer greasy.
- 4 The sample is partly gellable and partly water insoluble. The sample is more transparent than untreated fibre and have a very high cohesion. If pressure is put on the fibres, clear fibres, "dry fibres", can be seen. It may be possible to separate single fibres from the sample.
- 20 5 The sample is water insoluble with only minimal swellability.

In the wound care device according to the present invention the preferred cohesion of the modified chitosan fibre are in the area of 2 or 3 in the above categories. If a modified fibre sample evaluate to 2 or 3 removal in one piece seems to be possible.

Materials used in the samples:

Chitosan fibres from R C Bio-chemical Co. Ltd., Pusan, South Korea

(The fibres have a degree of deacetylation of above 90 % and the mole weight is from 50.000 - 200.000).

- 5 Chitosan powder (TM 370, particles < 100 micro) from Primex ingredients, Norway
 - 100 % acetic acid (glacial) from Merck.
 - 90 % lactic acid from Merck.
 - Sodium hydroxide from Merck.
- 10 Calcium alginate fibres (SeaSorb filler) from Coloplast A/S, Denmark
 - Carboxy methyl cellulose fibres (Aquacel) from ConvaTec, Ltd, UK.
 - Distilled water.
 - 96 % Ethanol from Danisco, Denmark.
 - 1-Propanol from Merck.
- 15 1-Butanol from Merck.
 - Solution A (142.5 mM NaCl and 2.5 mM CaCl_2 in distilled water).

EXAMPLE 1a:

Chitosan fibres treated with combined acid and heat.

- In a reaction vessel 200 grams of 96 % ethanol was mixed with 12 grams of
- 20 water and 150 mmole acid. To this solution 20 grams of chitosan were added and the suspension was treated at the boiling point of the suspension for app. 4 hours under reflux. The fibres were then washed twice in ethanol. Each sample was sterilised by 1*30 kGy electron beam. Hereafter the absorption and cohesion of the fibres were measured.

- 25 Table 1 is showing the absorption and cohesion of the samples, measured on sterilised samples. The absorbency was measured as double measurements.

TABLE 1:

Sample	Mole % acetic acid*	Absorption (g/g) 1 hour	Absorption (g/g) 24 hours	Cohesion (category)
1a	0	29	56	1-2
1b	10	37	55	2
1c	20	22	50	2-3
1d	30	21	31	3
1	50	12	12	4
1f	80	8	8	5
1g	100	4	4	5

* Of total acid content. The remaining acid content was lactic acid.

The dry modified chitosan fibres were relative soft and suitable for incorporation
5 in wound care devices such as wound dressings.

Example 1a is showing, that the higher concentration of acetic acid used in the
treatment of the fibres, the less absorbent and the more insoluble the fibre
becomes. The optimal wound dressing has a maximum absorption, but just
enough acid of the second type which gives the fibres insolubility, so the wound
10 dressing can be removed in one piece from a wound.

EXAMPLE 1b:

Preparation of a wound dressing.

A tow of sample 1c (non-sterile) was cut to 50 mm lengths and a wound dressing
was formed by first carding the cut fibre to form an approximate 20 g/m² web,
15 then cross folding the this web needling to provide a resultant non-woven fabric of
approximately 100 g/m², then a 10 cm x 10 cm square was cut to form the fabric.
The fabric square was packaged and sterilised using an electron beam dose of
30 kGy.

The non-woven wound care product had an absorbency of 51 g/g and 0.52 g/cm².

Alternatively the tow itself may be cut for example to 40 cm lengths, packed and sterilised. Hereafter it may be used as a wound cavity filler.

5 EXAMPLE 2a:

Chitosan fibres treated with acid and heat.

In a reaction vessel 200 grams of 96 % ethanol was mixed with 150 mmole lactic acid. To this solution 20 grams of chitosan were added and the suspension was treated at the boiling point of the liquid for app. 4 hours under reflux. The fibres
10 were then washed twice in ethanol. The sample was sterilised by 1*30 kGy electron beam. Hereafter the absorption and cohesion of the fibres were measured.

Table 2 is showing the absorption and cohesion of the sample (measured as triple measurements).

15 TABLE 2:

Sample	Absorption (g/g) 1 hour	Absorption (g/g) 24 hours	Cohesion (category)
2	27	47	2

The modified fibres were soft and flexible and very suitable for wound dressings.

Example 2 demonstrates, that the amount of water has an limited influence on both the absorption and cohesion of the fibres, when they are treated at the
20 boiling point of the ethanol. When the fibres are treated without additional water in the reaction vessel, the absorption decreases and the cohesion increases slightly.

EXAMPLE 2b:

Preparation of a non-woven fabric.

- A non-sterile sample of sample 2a was cut to 50 mm lengths and a wound care device was formed by first carding the cut fibre to form an approximate 20 g/m² web, then cross folding the web needling to give a resultant non-woven fabric of approximately 100 g/m², then a 10 cm x 10 cm square was cut to form a fabric. The fabric was packed and sterilised using an electron beam dose of 30 kGy.

The non-woven wound care product had an absorbency of 49 g/g and 0.49 g/cm².

- 10 Alternatively, the tow itself is cut for example in 40 cm lengths, may be packed and sterilised. Hereafter it may be used as a wound cavity filler.

EXAMPLE 3:

Chitosan fibre treated with acid at low temperature and subsequently heat treated.

- 15 Solutions containing 50 gram 96 % ethanol, 2.5 gram water and 35 mmole acid (mixtures of acetic and lactic acid) were prepared. To these solutions, 5 gram chitosan fibre sample was added and the samples were treated in the solutions at room temperature for 24 hours. Then the fibres were rinsed in 96 % ethanol and dried. When the samples were dry, they were heat treated for 6 hours at 100 °C
- 20 in an oven. Finally, the samples were sterilised by beta irradiation (1*30 kGy).

The absorption and cohesion of the samples were measured and the result is shown in Table 3 (based on triple measurements).

TABLE 3.

Sample	Mole % acetic acid*	Absorption (g/g) 24 hours	Cohesion (category)
1a	100	12	4
1b	80	15	2
1c	60	9	1
1d	20	0	0
1e	0	0	0

* Of total acid content. The remaining acid content was lactic acid.

This example also shows, that the optimal quantity of the first acid is not is the same for chitosan fibres treated with acid and a subsequently heat treatment, as for fibres treated with heat during the acid treatment. When the chitosan fibres are treated with acids at low temperature, with a subsequent heat treatment of 100 °C, the amount of the first acid should be kept below 40 %.

EXAMPLE 4:

- 10 Chitosan fibre treated with acid at low temperature and a subsequent heat treatment.

A solution containing 100 gram 96 % ethanol, 5 gram water, 2 gram acetic acid and 0.8 gram 90 % lactic acid was prepared. To this solution, 5 gram chitosan fibre sample was added and the sample was treated in the solution at room temperature for 1 hour. After the treatment the fibres were rinsed in 96 % ethanol and dried. When the sample was dry, it was heat treated at different temperatures and periods in an oven. At last the samples were sterilised using beta irradiation (1*30 kGy).

Table 4a is showing the absorption after 24 hours of the samples heat treated at different temperatures and periods.

TABLE 4a:

Temp.	80 °C	110 °C	140 °C	170 °C
Time				
0 minute	17			
1 minute	X*	X	X	15
2 minutes	X	X	X	16
5 minutes	X	X	X	11
15 minutes	X	X	18	11
½ hour	X	15	11	9
1 hour	14	15	9	< 10
2 hours	13	16	16	< 10
4 hours	12	15	12	X
8 hours	13	15	< 10	X

* When X is stated, the absorption was not measured

Table 4b shows the cohesion of samples heat treated at different temperatures and times.

5 TABLE 4b

Temp.	80 °C	110 °C	140 °C	170 °C
Time				
0 minute	0-1			
1 minute	X*	X	X	2-3
2 minutes	X	X	X	3
5 minutes	X	X	X	4
15 minutes	X	X	3	4
½ hour	X	3	3-4	4-5
1 hour	2	3	4	5
2 hours	3	3-4	4	5
4 hours	3	3-4	4-5	X
8 hours	3	4	5	X

* When X is stated, the cohesion was not measured

This example demonstrates, that when the fibres are acid treated at low temperature, a subsequent heat treatment is needed to make the modified chitosan fibres gelling and insoluble in water. If the fibres not are heat treated, they will dissolve
5 when they contacted with water or exudate.

The more severe heat treatment the more water insoluble the chitosan fibres will become. There is also a tendency for less absorbent fibres using a severe heat treatment.

EXAMPLE 5

10 The influence of the quantity of acid in the heat treatment .

In a reaction vessel 200 grams of 96 % ethanol was mixed with 6 grams of water and different amounts of lactic acid (see table 5). To this solution 20 grams of chitosan fibres were added and the suspension was treated at the boiling point of the non-solvent for app. 4 hours under reflux. Then the fibres were washed twice
15 in ethanol. The samples were sterilised by 1*30 kGy electron beam. Hereafter the absorption and cohesion of the fibres were measured.

Table 5 is showing the absorption and cohesion as a result of the quantity of acid in the combined acid and heat treatment (the results are a average of 3 measurements).

20 TABLE 5.

Sample no.	Gram 90 % lactic acid in the solvent	Mmole lactic acid per gram chitosan	Absorption (g/g)	Cohesion (category)
5a	16	8	53	2
5b	10	5	16	3-4
5c	6	3	12	4

To obtain highly absorbent fibres, more than 5 mmole lactic acid per gram chitosan is needed. To obtain fibres with high cohesion, the amount of acid should be minimised to below 8 mmole lactic acid per gram chitosan.

EXAMPLE 6

5 Use of different non-solvents in the acid treatment.

A sample was treated as in example 5a, except that 1-propanol or 1-butanol was used instead of 96 % ethanol. Each non-solvent was prepared in such a manner, that there was 7 grams of water per 100 gram alcohol. The acid treatment was carried out at the boiling point of the non solvents for app. 4 hours. After the treatment the samples were washed and sterilised. The absorption and gellability were measured. The results can be seen in Table 6.

Table 6 is showing the absorption and cohesion as a results of the used non-solvent in the combined acid and heat treatment (the results are a average of 3 measurements).

15 TABLE 6

Sample no.	Used non-solvent	Boiling point of non-solvent (°C)	Absorption after 24 hours (g/g)	Cohesion (category)
6a	Ethanol	78	53	2
6b	1-Propanol	97	48	2-3
6c	1- Butanol	117	43	3

These results show, that the higher boiling point of the non-solvent, the lower cohesion of the modified chitosan fibres is obtained. The results demonstrates further, that when the fibre are treated in non-solvent with a high boiling point, the absorption is minimised, if the process time is constant.

EXAMPLE 7

4 grams of sample 5a (non-sterile) was mixed by carding with different quantities of calcium alginate fibres or carboxy methyl cellulose fibres. The fibre mixtures were sterilised (1*30 kGy). The absorption and cohesion of the sterile samples were measured.

Table 7 demonstrates the absorption and cohesion for fibre samples comprising mixtures of anionic and modified chitosan fibres (the results are averages of 3 measurements).

TABLE 7.

Sample no.	Type of anionic fibre	Quantity of anionic fibre (grams)	Absorption after 24 hours (g/g)	Cohesion (category)
7a	Calcium Alginate	4	36	3
7b	CM-Cellulose	4	35	3
7c	CM-Cellulose	1	34	3

This example shows, that if the chitosan fibres are mixed with alginate or carboxy methyl cellulose fibres, the cohesion of the fibres increases; while the absorption decreases.

EXAMPLE 8

Chitosan fibre treated with acid at low temperature and a subsequent heat treatment.

A solution containing 100 gram 96 % ethanol, 5 gram water, 6.4 gram 90 % lactic acid and 1.0 gram acetic acid was prepared. To this solution, 10 grams of chitosan fibres were added and the sample were treated in the non-solvent at room temperature for 1 hour. After the treatment the fibres were rinsed in 96 % ethanol and dried at 30 °C. When the samples were dry, the sample was treated with heat. The heat treatment was carried out at different temperatures and periods in

an oven. After the heat treatment the samples were sterilised using beta irradiation (1*30 kGy).

Table 8a demonstrates the absorption and cohesion (absorption (g/g) / cohesion) of the samples heat treated at different temperatures and periods (measured as a triple measurement on sterile samples).

TABLE 8.

Temp. Time	110 °C	135 °C	160 °C
0 minute	soluble		
2 minutes	x	x	soluble
8 minutes	x	soluble	44/2
20 minutes	x	soluble	40/2-3
1 hour	10/1	27/2	17/4
4 hours	10/1	23/3-4	x

The results demonstrate, that the higher temperature the subsequent heat treatment is processed at, the higher absorption is obtainable. Also the duration of the heat treatment is influenced by the heat treatment (the higher temperature, the shorter time is needed to obtain insoluble fibres).

EXAMPLE 9

Chitosan fibre treated with different quantities of acid at low temperature and a subsequent heat treatment.

- 15 The samples were processed as in Example 8, but with following adjustment:
In Example 9a the only used acid was lactic acid (8 gram 90 % lactic acid per 10 gram chitosan), and in Example 9b the acid volumes were 4.8 grams 90 % acetic acid and 2 grams acetic acid.

After acid treatment both samples were heat treated at 160 °C for 10 minutes. Hereafter the absorption and cohesion was measured.

The absorption and cohesion result are listed in Table 9.

TABLE 9

Sample no.	Absorption after 24 hours (g/g)	Cohesion (category)
9a	43	2
9b	27	3

5

This example is showing, that when the chitosan fibres are modified in a two step process (acid treatment at room temperature and subsequently a heat treatment), only one acid is needed to obtain fibres with cohesion enough to removal in one piece is possible. The example also demonstrates, that the more acetic acid in
 10 the treatment, the higher cohesion is obtained, but the absorption decreases with increasing amounts of acetic acid.

EXAMPLE 10

Preparation of a woven fabric comprising chitosan fibres.

The modified chitosan fibres (sample 9a in Example 9) were processed into yarn,
 15 and a woven fabric was made. The material was cut in squares of 10*10 cm², packed and sterilised.

The woven fabric is suitable as a wound care device, to cover and gel upon a wound site while absorbing a high amounts of wound exudate.

EXAMPLE 11

20 Preparation of a woven fabric comprising chitosan fibres and cotton.

The modified chitosan fibres (sample 9a in Example 9) were processed into yarn and weaved with cotton to produce a woven fabric (40 % chitosan and 60 % cotton). The material was cut in squares of 10*10 cm², packed and sterilised.

The woven fabric is suitable as a non adherent wound dressing to place directly
5 on a wound and protect the wound against the secondary wound dressing and from drying out.

EXAMPLE 12

Comparing treated fibres and powder.

10 grams of chitosan powder was treated as the fibres in sample 1c (but not
10 sterilised). Figure 1, a colour photo, shows the difference in cohesion between powders and the fibres prepared according to this invention (the fibres and powder are treated exactly the same way and both samples are non-sterile). The figure shows both the fibres from sample 1c (non-sterile) and the powder prepared as sample 1c.

15 The powder is discrete insoluble absorbent particles, while the fibres turns into a cohesive mass. Thus, this example demonstrate that the cohesion may only be obtained by the use of fibre, while the same effect will not be achieved by using powderous chitosan. The powder particles are not suitable as the main ingredient in a wound care product if removal in one piece is desired, while the fibres indeed
20 are useful as the main ingredient in a wound care device.

EXAMPLE 13

The maximum absorbency of some selected fibre from the earlier examples.

The maximum absorbency is measured after 3 days in solution A after the same method as absorption after 24 hours. The absorption is measured on non-sterile
25 samples.

TABLE 13

Sample no.	Absorption after 24 hours (g/g)	Maximum absorp- tion (g/g)	Cohesion (category)
5a	53	70	2
6b	48	47	3

- This example is showing that the absorption is increasing in up to 3 days when the cohesion is evaluated to 2. If the cohesion is evaluated to 3, the maximum
- 5 absorption is reached within the first 24 hours. Samples with lower cohesion may have higher absorption. This is due to the samples swellability, which is higher, when the sample is less cohesive.

EXAMPLE 13b

- A non-sterile sample of sample 5a and of 6b was cut to app. 50 mm lengths and
- 10 a wound dressing was formed by first carding the cut fibre to form an approximate 20 g/m² web, then cross folding the this web needling to give a resultant non-woven fabric of approximately 100 g/m², then a 10 cm x 10 cm square was cut to form the fabric. The square of the fabric was packaged and sterilised using an electron beam dose of 30 kGy.

- 15 The sterile non-woven wound care device of sample 5a had an absorbency of 60 g/g and 0.59 g/cm².

The sterile non-woven wound care device of sample 6b had an absorbency of 46 g/g and 0.48 g/cm². The wound care device is easily removed in one piece from a exuding wound.

20 EXAMPLE 14

Prolonged acid treatment.

A sample was treated as sample 1a, but the acid treatment was prolonged to 10 hours instead of 4 hours.

The absorption and cohesion is listed in table 14 (as a average of triple measurements).

TABLE 14.

Sample no.	Absorption after 24 hours (g/g)	Absorption after 3 days (g/g)	Cohesion (category)
14	55	74	2

- 5 This example demonstrates, that only one acid is needed in the acid treatment when the is conducted at the boiling point of ethanol (below 85°C). It is possible to prepare modified chitosan fibre samples with extremely high absorption compared to prior art.

EXAMPLE 15

- 10 This example demonstrates the method of making suberabsorbent gellable, substantially water insoluble modified chitosan fibres by partly carboxy methylating the chitosan fibres. A solution containing 100 gram water, 15 gram sodium hydroxide, 45 gram sodium chloro acetate and 100 gram of ethanol was prepared. 10 grams of chitosan fibres were added to the solution and the solution
- 15 was heated to the boiling point of the solution and treated until the fibre was partly carboxy methylated. After the treatment, the modified chitosan fibres was washed in an alcohol bath containing an acid. The fibres were finally dried.

The fibres were processed into an sterile non-woven fabric (as in Example 1b).

CLAIMS

1. A wound care device comprising chitosan, said chitosan being capable of absorbing liquid to form a swollen, coherent gel, and said chitosan being in the form of fibres having been modified by treatment with acid and heat.
- 5 2. A wound care device according to claim 1, characterised in that the chitosan has a molecular weight of less than 750.000, more preferred less than 400.000 and most preferred less than 250.000.
3. A wound care device according to claim 1 or 2, characterised in that the proportion between length and diameter of the fibres is at least 25, more
10 preferred more than 80 and most preferred more than 200.
4. A wound care device according to any of claims 1 - 3, characterised in that the chitosan fibres have an absorption higher than 20 g/g, more preferred higher than 25 g/g and most preferred higher than 30 g/g.
5. A wound care device according to any of claims 1 - 4, characterised in that the
15 acid is an hydroxy or acyl organic acid, which is soluble in the solvent used, preferably glycolic, glyoxylic, pyruvic, lactic or a hydroxy propionic/butanic acid.
6. A wound care device according to any of claims 1 - 5, characterised in that the heat treatment of the chitosan is carried out at a temperature of 50 - 250°C.
7. A wound care device according to any of claims 1-6, characterised in that the
20 fibres are manufactured into a fibre rope, knitted, woven or non-woven sheet or pouch or in the form of an island dressing.
8. A wound care device according to any of claims 1 - 7, characterised in that the device comprises from 0 - 60 % of fibres other than chitosan.

9. A wound care device according to any of claims 1- 8, characterised in that the acid is a mixture of at least two acids.

10. A method of preparation of a wound care device comprising chitosan being capable of absorbing liquid to form a swollen, coherent gel, said method

5 comprises the steps of

- a) suspending the chitosan in the form of fibre in a non-solvent comprising acid
- b) isolating the resulting modified chitosan from the non-solvent
- c) treating the chitosan with heat during step a) or/and b).

ABSTRACT**Wound Care Device**

Wound care device comprising chitosan, said chitosan being capable of absorbing liquid to form a swollen, coherent gel, and said chitosan being in the form of
5 fibres having been modified by treatment with acid and heat.

Figure 1

